Valve disease is common. The population prevalence of moderate and severe disease in the USA is 2.5% (1). It is also potentially fatal (1) but expensive to treat invasively. Recently there have been major advances both in surgical repair and transcatheter techniques, but uncertainties remain about when these should be used. Insufficient information exists about the basic biology and physiology of valve disease to guide research on medical methods to reduce the progression of valve disease or delay the need for surgery. The most recent survey by the Society of Cardiothoracic Surgeons of Great Britain and Ireland (SCTS) confirms continued variability in access to appropriate specialist care for valve disease and we need to discuss better ways of delivering this care. In this review we discuss what is known about valve disease and what important gaps in clinical knowledge remain and which might be amenable to research.

Timing of surgery in native valve disease

There is good agreement that surgery is indicated for patients with symptoms or with early impairment of LV function (2,3). However early LV dysfunction is traditionally defined by a reduced ejection fraction which is known to be potentially misleading. We need to investigate the predictive power of early markers of LV dysfunction notably reduced contractile reserve and biomarkers including B-type natriuretic peptide (4).

In aortic stenosis, the mechanism of symptom production is not fully-established and this requires further work using advanced imaging techniques during exercise. There are nonrandomised studies showing that early surgery is likely to be better than watchful waiting in patients with critical disease (5,6). However there is still uncertainty about timing of surgery in asymptomatic patients with subcritical disease (transaortic peak velocity 4.5-5.5 m/s) or the elderly aged > 75 with critical disease (transaortic velocity > 5.5 m/s) in whom surgical risk is still not negligible (7). The European (3) but not American guidelines (2) suggest that significant LV hypertrophy should be a criterion for surgery even in the absence of symptoms, but there is also work suggesting that the development of moderate diastolic dysfunction is a better indicator than anatomical hypertrophy (8). This has never been investigated prospectively.

There is uncertainty whether immediate surgery (9) for repairable degenerative mitral valve disease is superior to ‘watchful waiting’ (10) and this could be resolved by an RCT. Particular concern over early surgery was raised by evidence of a high cumulative failure rate after repair (11), but this study included centres of varying experience and valves with pathologies other than degenerative disease. A registry of results after repair in the UK is required and an RCT of conventional and minimally invasive surgery in terms of cost-effectiveness, length of stay and clinical outcome.

Functional mitral regurgitation is difficult to treat and guidelines currently suggest that valve surgery should only be considered after failure of full medical therapy including resynchronization therapy (2,3). However LV remodelling with mitral annuloplasty even in patients with very low ejection fraction may produce good results with an early mortality 5-10% and 80% two year survival. We now need an RCT of mitral valve surgery (repair vs replacement) with or without LV remodeling vs full medical therapy in symptomatic functional mitral regurgitation.

Tricuspid valve surgery is seen as high-risk. However this is probably because intervention tended only to be attempted for tricuspid regurgitation occurring late after left-sided surgery as a last resort and in the presence of pulmonary hypertension and right ventricular failure. Results appear to be far better when performed for degenerative disease or relatively early in the natural history of rheumatic disease. A registry of tricuspid valve repair for degenerative disease is required as well as an RCT of tricuspid annuloplasty performed at the same time as left-sided valve surgery guided by annulus diameter on transthoracic echocardiography.
Medical treatments
There is almost no medical therapy recommended in valve disease other than nifedipine or angiotensin converting enzyme inhibitors which have been shown to delay the need for surgery in aortic regurgitation. There is early evidence (12) that beta-blockers reduce the regurgitant volume in mitral regurgitation and an RCT is needed to see if this translates into a delay in the need for surgery particularly in those at high risk of surgery. Beta-blockers and angiotensin receptor blockers reduce the risk of events from aortic disease in small populations with Marfan syndrome. However there is no equivalent information in bicuspid valve disease or arteriosclerotic aneurysms. It is uncertain whether a placebo-controlled trial would be ethical, but a comparison of beta-blocker with and without angiotensin receptor blockers would be acceptable.

No medication has yet been shown to improve the progression of aortic stenosis although there is some evidence that statins given in early thickening may be effective (13). An RCT of statins in very early disease would therefore be ideal required. There is also early evidence that angiotensin converting enzyme inhibitors and anticalcific treatment may be effective. Probably the most useful approach would be a placebo-controlled study of a combination of angiotensin converting enzyme inhibitor, statin, and calcium modulator.

Replacement valves
Some 12,000 replacement valves are implanted each year in the UK. No replacement valve is exactly equivalent to a normal native valve and all have potential adverse effects. A CE mark is awarded if adverse events do not occur more frequently than expected for an industry standard after follow-up for 400 patient-years. This does not exclude uncommon events or premature valve failure occurring beyond about 4 years after implantation. Recently withdrawn valves include the St Jude Medical Silzone and Cryolife-O’Brien stentless prosthesis. We need a registry to alert us to unexpected early failures. Furthermore, there is no systematic analysis of valve failures as was previously available from Sheffield University and this needs to be restarted. If valves are examined locally or sent to individual manufacturers it will be impossible to build up a coherent and independent view of failure rates and modes. Ideally controlled trials of all new heart valves introduced on the market vs industry standard should be conducted at designated centres to allow further clinical hemodynamic and safety data to be collected.

A major disadvantage of mechanical valves is the need for warfarin. However there is early evidence that newer bileaflet replacement valves in the aortic position can be managed on low levels of anticoagulation and potentially on antiplatelet therapy alone. Larger trials of low anticoagulation levels or antiplatelet therapy only in mechanical valves are now needed together with studies of new anticoagulants e.g. dabigatran.

There is a small risk of valve thrombosis in stented biological replacements usually early after implantation. It is not known whether early anticoagulation with warfarin is superior to aspirin nor whether antithrombotic agents can be stopped after three months.

Early pannus may be difficult to detect on echocardiography and there is early work suggesting that CT may be more useful. However experience is anecdotal and a registry is need comparing CT and echo vs surgical finding.

Endocarditis
There is no RCT of antibiotic prophylaxis before dental work and the lack of proof of efficacy was one of the reasons that NICE has advised the avoidance of virtually all prophylaxis. This is contrary to guidelines in the rest of the world which makes the UK a natural test-bed for an RCT. This would be most practicable in patients with high risk (prior endocarditis or prosthetic heart valves) having high-risk dentistry (e.g. extractions). Until this reports it would be useful to have a registry to examine timing of new cases of endocarditis relative to dentistry. Ideally these cases should be included in a national case control study. It would also be useful to conduct a simple survey to determine how often NICE guidelines are used in place of European or American guidelines.
In treating endocarditis mortality has improved with early diagnosis and surgery, but it is still high. Uncertainty remains about the timing of surgery with a relatively high incidence of surgery required after discharge following the initial illness. We need an RCT of immediate surgery vs conventionally indicated surgery in high risk groups e.g. Staph aureus on left-sided valves, or with embolism at presentation, or the presence of moderate or severe regurgitation.

Epidemiology/Natural history
The prevalence of valve disease is thought to be high throughout the West but this is based on studies in the USA and Finland. It would be useful to confirm these within the UK. OxValve is already in progress, but this could be extended to the rest of the country. The prevalence of rare causes of valve disease e.g. carcinoid is not reliably known and this should be the subject of a registry. There are anecdotal reports of rheumatic disease occurring in young people who have never left the UK and it would be important to record how common this is in a national registry. A number of patients still present with organic valve disease of uncertain aetiology and these should be collected to see whether a cause emerges with the examination of a series.

The natural history of valve disease was largely determined in the early part of the 20th century. However early valve disease is increasingly detected with new imaging techniques and the natural history of mild disease, for example bicuspid aortic valve without stenosis or regurgitation is not known and has an important bearing on frequency of follow-up and screening. A related question is how common aortic dilatation develops late after valve replacement for a bicuspid aortic valve since this affects the frequency of follow-up.

Basic biology/physiology
The early lesions of aortic stenosis are known to resemble atheromatous disease in the aorta or coronary arteries, but the role of subsequent angiogenesis, inflammation, and ion and calcium metabolism requires further elucidation. This might lead to treatments to modify the natural history.

The genetics and embryology of valve disease is poorly understood and collation of genetic analysis from established biobanks and twin-studies may suggest new determinants of the presence of disease or its progression and LV adaptation leading to possible preventive strategies. The genetics of LV fibrosis and hypertrophy is inadequately described and the interplay between genetic and environmental factors requires investigation.

Recent work shows that there is coupling between the aortic valve and aorta which should be considered a single physiological unit. The implications of this in terms of coronary flow, exercise capacity or the mechanism of symptom-production are not known. Aortic compliance is likely to be an important determinant of outcome in patients after transcatheter procedures (TAVI) who have significant but not critical aortic stenosis and this has not been investigated. The immediate effects of TAVI on aortic flow and long-axis and diastolic LV function and on LV biochemistry needs to be investigated.

Political/organisational
The cost to the economy of valve disease is not known and a registry of health economics outcomes is needed in sample populations throughout the UK. The SCTS registry has already identified major variations in access to valve surgery across the country and availability of specialist surgery notably of mitral valve repair (14). The reasons for this need to be explored. A pilot study of auscultation by GPs in people aged > 65 or 70 to determine how reliably valve disease can be detected would inform the organization of medical investigation. Specialist valve clinics are being developed (15) and an analysis of different models is required to determine national guidelines for diagnosis and surveillance of valve disease. Results from these descriptive studies would also answer a number of practical concerns e.g. do mechanical aortic valve replacements need regular follow-up or is discharge to the community reasonable.
Specialist centres for clinical follow-up and valve surgery are widely seen as essential (Bridgewater), but no data supporting this exist. It would be possible to compare outcome in high volume specialist centres vs the average from the SCTS report. Developing processes /pathways to maximise repair rates remains important.

Conclusion
One of the reasons for the founding of the BHVS was to improve awareness of valve disease and to foster collaborative research. The current situation gives cause for concern. Basic information about the epidemiology of valve disease in the UK or its economic cost is not available. We do not even know how many hospitals use the NICE or international guidelines for antibiotic prophylaxis. Surveillance of new designs of replacement heart valve or of new cases of endocarditis does not exist. The SCTS report makes us aware of wide variations in access to specialist care but not the reason for this variation. Our knowledge of the genetics and biology of valve disease remains elementary. Treatment studies have mostly relied on small populations without control or randomization. The areas of clinical ignorance or uncertainty which we describe are large. They will yield to research but will also require the collaboration of government and regulatory bodies.

References
